then how many patients do we have to study to make sure it's safe? Those would be the two questions, I think, that are most important. Am I wrong?

MR. DILLARD: Jim Dillard. I think you did a real nice job summarizing that. Thank you.

DR. BAILEY: I'm happy with pain relief, is where I'm at. It's a perfectly fine clinically relevant endpoint. But I worry then if you can't get the masking what the conclusion is if you find significant pain relief but the patient is aware that they've got something happening. I mean, maybe that's okay, as Dr. Domanski said. Maybe the placebo effect is--if this is one way to deliver a placebo, great. But I think it would be important to know that.

CHAIRPERSON CURTIS: Well, I think if you had some objective measure of ischemia and you learned the answer, yes, it improves, no, it doesn't change, or whatever--

DR. BAILEY: You don't need it to improve ischemia. I mean, I would just like an objective measure that it really does improve pain--

CHAIRPERSON CURTIS: How are you going to do that?

DR. BAILEY: --without a placebo effect?

DR. DIAZ: There is no way to measure objectively pain improvement. It's purely a subjective concept.

CHAIRPERSON CURTIS: I think that's why the thought about getting some measure of ischemia in there.

DR. BAILEY: But if you require ischemia, then you're saying pain relief is not enough.

CHAIRPERSON CURTIS: I think that's more of a mechanistic look at it. You know, why is it or, you know, partly the safety, which you mentioned before, but partly just, you know, can you see that there's a change in ischemia to go along with the observation. And if there were, you know, you might actually get at a claim that, yes, it relieves ischemia and improves pain. If it doesn't, then you're only going to be able to say pain relief.

DR. BRINKER: Well, you could help objectify pain relief with an exercise test. It's a functional assessment that has nothing to do necessarily with ischemia.

DR. VETROVEC: I do think, though, that the next question which deals with safety will come back to the ischemia, because we're not going to have a finite follow-up period in these patients, or at least a long follow-up period, almost surely. And the length of the follow-up to judge safety may be partly determined on how much ischemia relief they get a well as pain relief. If one things about giving a patient morphine and exercising them and they don't get any pain and they can go a lot further, we would at least intuitively think that they're at greater risk over some amount of time, and maybe that follow-up time needs to be greater. Whereas, if you see ischemia relief plus pain

relief, you'd be much more comfortable with a shorter follow-up period.

DR. DIAZ: Exactly.

CHAIRPERSON CURTIS: Perhaps this would be a good time to take a break. Let's take a 15-minute break and reconvene at 10:40.

[Recess.]

CHAIRPERSON CURTIS: I want to finish up over the next few minutes on Question 2, and I think the last thing we need to discuss is the follow-up duration necessary to capture a clinically meaningful benefit, as I said, taking into consideration the duration of the placebo effect.

We talked about quality of life, we talked about exercise treadmill time, and then we had some discussion about objective measures of ischemia. If I could take quality of life, because that was a pretty good consensus primary endpoint.

What kind of follow-up duration do you need to capture a meaningful effect, particularly considering that we were talking about various designs where patients would be crossing over from different treatments? Any comments on that? And can you tell an effect on quality of life in a month, in two months, in three months?

DR. BAILEY: You know, I think if you have the confidence in the control and the masking, you could detect

it right away, and then the question is does it last.

DR. SIMMONS: There has to be some diminution of the placebo effect after a period of time, too, doesn't there? I mean, if you're going to follow somebody for six months, the initial joy of having a device implanted has got to go away sooner or later. There's got to be a minimum time of follow-up just to see at the end of six months or a year, I would say.

CHAIRPERSON CURTIS: I agree. And I guess one of the things that I was a little bit concerned about, getting overly complicated about crossing over in doses and all the rest of that is having a duration of time to have the effect, having a washout period, and then coming back with another kind of programming, or however you wanted to turn the device on, and also being able to measure that. I would think you might be looking at something like three months for a duration of therapy with a--let's argue that. Let's say you did three months and then had a month washout period and came up with another three months of something else you did.

You could do that, have three different therapies per patient, and get that all done within a year. You know, and I don't know that any of us would want to argue for a study duration that went longer than that.

DR. HARTZ: You could actually have four

therapies, because if you did a two-month and a one-month washout and then another one, you could almost be getting dose, but a year's probably the maximum.

CHAIRPERSON CURTIS: Yes. So maximum of a year, and somewhere along the lines of two to three months per treatment period would be reasonable in terms of looking at that?

[No response.]

CHAIRPERSON CURTIS: No arguments. Okay. Well, then, let's barge ahead to Question 3.

MR. DILLARD: Dr. Curtis?

CHAIRPERSON CURTIS: Yes?

MR. DILLARD: Sorry. Jim Dillard. Before we move on, could I just--Mitchell, if you could put that back--ask one other real quick question I think you can quickly answer? In terms of quality of life, would there be any difference in terms of a more objective measure perhaps, as I heard one of your recommendations to be, to perhaps include an objective measure here, perhaps a functional measure? How would that factor in if the primary endpoint were quality of life and if we were going in a two- or three-month kind of time frame that you just recommended? How does that factor in? Does it factor in any differently? Or should there be something else we should consider?

CHAIRPERSON CURTIS: I would think changes in

treadmill time would probably occur fairly quickly. I would do the treadmill at the end of the treatment period. So I don't think that has to affect you. I think if you were only looking at treadmill time, you could easily do it after two or four weeks of therapy. So if you did it after two or three months, I don't think that matters. I think we just, you know, have to be careful that if you talk about quality of life, it is hard to assess that in a very, very short period of time. So I think you have to look over a little bit longer haul there.

DR. BRINKER: Could I ask just a question or two here? When you do the treadmill, I presume that the device is activated even if--in your particular study, if they were on for three hours a day or whatever, when they did the treadmill, it was placed on. And so one of my questions would be the effect, once you put it on, is immediate in terms of pain relief. So I think that while the duration of effect after it's turned off may be up for grabs, I think it's a pretty good assumption that when you turn it on, the effect is immediate. Okay. Thanks.

CHAIRPERSON CURTIS: Which could argue for an even shorter period of observation. Maybe two months is more than enough.

Any other issues?

[No response.]

MR. DILLARD: Thank you.

CHAIRPERSON CURTIS: Number 3, this is the safety discussion. Safety endpoints that would be important to consider during a clinical investigation and the follow-up duration necessary to capture the safety endpoints. So there are going to be some obvious ones related to the lead itself, lead migration, infection, breakage, battery failure. Battery failure is something that's probably like to go longer than a duration of a study. It's probably going to be something you see past a year's follow-up time. But the other ones are things that could be seen early on.

We also had some discussion about death and myocardial infarction as safety endpoints, although you'd have to have a very large number of patients in order to really look at death, unless there was a huge difference between the patient groups.

In terms of lead-related issues, duration of study? I work think a year would be what you'd probably be looking at. You can't pick up late lead failures and things like that, but you could pick up early problems with lead migration. Any comments?

DR. CHANG: Isn't there a piece of lead after three months or so it will fibrose and it will not migrate?

CHAIRPERSON CURTIS: Can you get late lead migrations?

DR. DeJONGSTE: There is some fibrosis but not very heavily, as you have a high increase in impedance. But I think you have to distinguish between dislodgment and micro-dislocation because the lead will sometimes have a micro-dislocation, and then because you have quarter re-polar(?) links, you can easily switch and have another bipolar stimulation. So you have to choose then if you take that into account, if you see that as a complication, that there is a reprogramming of the device due, for instance, to micro-dislocation. It is very difficult to demonstrate. Even with CT scans, it's difficult. Or you just go for major complications.

DR. CHANG: But that's not as important as pacemaker leads?

DR. DeJONGSTE: No.

DR. CHANG: So it would not be a concern at all?

DR. DeJONGSTE: The capture here is very subjective. It depends on what the patient reports.

CHAIRPERSON CURTIS: Do patients new re-operations for lead-related problems?

DR. DeJONGSTE: Sometimes, if there is a major lead problem, yes. Lead fracture, for instance.

CHAIRPERSON CURTIS: And how often have you seen that happen?

DR. DeJONGSTE: We saw that in the beginning when

we started with the therapy in '86. We saw that often happens because we have unipolar leads and you have not the option to change the electrode position. And now it's diminished. It was quite a few in the beginning. It's difficult to recall that, but it's now--lead migration is, say, 5 percent, I don't know, just a rough estimate.

CHAIRPERSON CURTIS: Okay.

DR. VETROVEC: You can program the different electrodes that are in use, so you don't have to switch electrodes.

DR. DeJONGSTE: Yes, and we started always after the operation bipolar, to treat bipolar, because unipolar in the suture, the wound, when it's healing it's painful for the patient. So we started bipolar, and then we usually switch to unipolar because that is saving energy.

DR. HARTZ: Have you had any epidural hematomas?

DR. DeJONGSTE: Never.

DR. HARTZ: Have you implanted anyone on Coumadin?

DR. DeJONGSTE: Pardon?

DR. HARTZ: Who has been on warfarin.

DR. DeJONGSTE: Yes, there must be. I can't recall that, but there must be.

DR. HARTZ: I think that should be a warning.

DR. DOMANSKI: Well, I guess the question is: Why should it be a warning? You know, it does that--unless

you've got some evidence that there's a risk to it, then I wouldn't--certainly wouldn't start labeling based on a guess.

DR. DeJONGSTE: We stopped the aspirin and the warfarin ten days--aspirin ten days prior to the procedure.

DR. DOMANSKI: When would you restart Coumadin?

DR. DeJONGSTE: I guess the same day, after the implant.

DR. DOMANSKI: I mean, I don't--

DR. HARTZ: It's just that no anesthesiologist would ever put an epidural catheter in an anti-coagulated patient.

DR. DOMANSKI: Oh, yes. I mean, I think for the procedure itself, the usual--you know, the usual precautions are--

DR. HARTZ: Sure.

DR. BRINKER: I mean, you put in a heart valve in somebody, and you don't put it in when they're on Coumadin, but certainly you wouldn't want to--you wouldn't want to say you can't put in a heart valve if the patient is going to be on Coumadin.

As a post-procedural--

DR. HARTZ: I'm thinking of a lead fracture.

DR. BRINKER: You mean after--I think we have to distinguish between procedural, which I think agrees nobody

wants to do any of this during an anticoagulated state, and then post-procedural. And what I'm hearing is that the risk of post-procedural phenomenon related to Coumadin would be very unlikely. And I think that if you're going to--if you have experience, it would be helpful for the sponsor to look up and see if there's experience--and I'm sure there is because this is a group of patients that may not infrequently be on Coumadin--that there is some patients that have had Coumadin after the procedure, and that would be all that would bother me, I think.

CHAIRPERSON CURTIS: Are there any other safety endpoints other than the ones that have been mentioned that anybody can think of that should be addressed?

DR. SIMMONS: I thought this was where we were going to address the issue of are you going to look at left ventricular function pre- and at a year and make sure that these patients aren't having infarcts and that's why they're not--

CHAIRPERSON CURTIS: Okay.

DR. SIMMONS: I mean, are you going to do a TEE? Are you going to do a PET scan or an echo or--I mean, all these patients should probably have some evaluation for ischemia and LV function pre- and post- a year just to make sure that the therapy isn't that we're just aligning them to infarct, I guess. Or maybe it doesn't matter, but--

DR. DOMANSKI: Yes, you could even do that pretty simply. I mean, it seems to me that in addition to mortality, LV function, and given the difficulty of echoing these people and the semi-invasiveness of doing a TEE, which doesn't do global stuff very well, anyway, a muga (?) scan would be something real simple and real cheap and a nice way to do it.

DR. BRINKER: What are you doing with that? Just seeing whether they've had a silent infarct?

DR. DOMANSKI: Yes, I think you are. I think if there were a material detriment in LV function in that group, then I'd be concerned, because, you know, the guy's out shoveling snow who's not having pain despite the fact that he's infarcting or, you know, having induced full ischemia, I guess I'd be concerned about--and it's a cheap test, really.

DR. BRINKER: At the end of a year, just looking to see if there was a change in ejection fraction.

DR. DOMANSKI: Yes, and I'm not sure what the time should be. It certainly shouldn't be less than a year.

DR. BRINKER: Well, that would be a very long study if it's--even a year is a long endpoint for that.

DR. BAILEY: Is there any way to look at function at each of the exercise tests?

DR. BRINKER: We have got to separate, I think,

ischemia from the--that's what we usually look at function for, you know, exercise-induced changes in function being ischemia, which I don't think is important. From this other issue about how can we be sure that a patient hasn't had a myocardial infarction, well, obviously, death is an easy endpoint to measure.

It seems to me an EKG is probably a good thing to have because that will pick up a significant--a Q-wave infarct, obviously. I guess there is a potential that there could be subtle changes in ejection fraction due to myocardial necrosis because of subendocardial infarction, but realize that you need a control group that would have--since these are high-risk patients with multiple procedures, if you wanted to do this at a year, you would have to have a control group at a year get the same thing. And I think that that's not likely to happen. I don't think we'd have a control group--I mean, you said yourself that the control group was somebody that got the device, you wouldn't want to keep them without therapy for a year.

DR. BAILEY: We're talking about a crossover study here, anyway, with the three or four different treatment groups. So you have to get the functional assessment at each period to see when the infarction occurred. It's not enough to know it occurred sometime during the year.

DR. BRINKER: Yes, it is. I mean, unless it--

because you don't know--no, sure it is. I mean, if you take the--the issue is: Does it occur? And if it does occur, it will occur--the longer your observation is, the more likely you'll pick up a difference.

DR. BAILEY: But each patient is exposed to no treatment and to treatment at some point during the year, so I don't see how one assessment at the end of the year tells you anything.

DR. BRINKER: Yes, but I think that if you only look for three months, you know, the only group that you will have as a control would be the initial group before crossover. And at three months, if that's the comparison, you have to--you have to compare them at the same time.

DR. DOMANSKI: I think probably everybody is saying the same thing--I think, anyway. Clearly, if you have a crossover design, he's right. I mean, if there's a crossover design rather than just randomization, then you need to do it before you start the next therapy or you don't know what caused it.

DR. BRINKER: Right, but there's only--

DR. DOMANSKI: So I think you're saying that, too.

DR. BRINKER: --one group that's not going to have any therapy, because we don't know whether low-dose therapy, for instance, in the treat--if that's the way you were going to go, you know, dose ranging, whether that has enough of an

effect.

What I'm saying is that the only way that you would be able to capture this is on the treated group versus the totally non-treated group at the get-go, and the non-treated group is only going to be observable for a relatively short time, three months. So even if you have a hundred patients in the control group at three months, that's only 300 months of follow-up, all front-loaded, and I don't think that would--look, even from the studies we have, these patients aren't dropping like flies or developing Q-wave infarcts in great numbers in a silent way. The likelihood of picking up something with a muga scan, a difference at a muga scan at three months is going to be negligible.

DR. DOMANSKI: Oh, I don't know. I guess what we're saying is, if there's a control group, of course, that never gets treatment, then that's obviously the group one would compare it to. But if everybody crossed over, then what one might expect is somebody went three months, let's say, with treatment, there's no infarct--or without treatment there's no infarct, and then you do, in effect, a second functional assessment, whether it's echo or muga. Then during the next period of time they're on treatment. After a period of time on treatment, one would look again at the functional assessment, and I think that--Kent, you

correct me, but I think you could do the statistics on that and figure out whether on or off treatment it's more likely that you're going to have a reduction in your left ventricular function.

The only other comment I'd make--and then I'll stop--is that I think, of course, the EKG is an obvious thing and it's got to be done. I think it's going to be a little less valuable in this group because many of them are people who have had multiple infarcts previously, anyway, and so that group, this sort of new Q-wave thing may be difficult to ascertain.

DR. BRINKER: Well, that's what--again, the way I've looked at this, only one group--any group that starts getting some form of treatment is not going to get crossed over to no treatment, I don't think. I think it's the group that got no treatment that's going to be crossed over--

DR. DOMANSKI: I'm not sure why not. I think you could probably cross them both ways, Jeff. I mean, they have the machine in and--

DR. BRINKER: Well, I was thinking more along the terms that if you were going to do--if you were going to use that group, I guess I'm still fixated on my concept that I'd like to use that group to do the dose finding study.

DR. DOMANSKI: No, I think that's another design. I mean, there are different designs. It's very hard--it's

going to be very hard in a day to sit here with a panel and design three trials in a final way. But I think we're putting together several options. Done your way, it's a little bit different, and that's fine, it's another design.

DR. BRINKER: Just from a priority point of view, I don't think that if it were done any other--that in a high-risk group, the occurrence of infarcts, even small infarcts, are going to be time-dependent, and that if you only get a snapshot of time, it's going to be very difficult to have any comparison.

DR. SIMMONS: But it sounds like it hasn't been done at all, so you don't know what the risk is going to be at all right now, do you?

DR. BAILEY: That's the whole idea of balancing it. If you balance it so that some people start out with treatment, some start out without treatment, and then switch, you balance it and then you can assess at the end of the day. You take account then of the changing, perhaps, trajectory of the risk over a year's time.

CHAIRPERSON CURTIS: I guess I think, too, that if you look at short periods of time, there's not likely to be a whole big effect here. And so I'm not sure how much I think that that needs to be measured that frequently, which is what I think Jeff was saying.

But if you did it at the beginning and at the end

of the trial, I guess--well, since all the patients would have had therapy at some point, I think the problem is that knowing what you would normally expect--let's say you took 100 patients who had intractable angina and you looked at their ejection fractions, and then a year later on their medical treatment you looked again, I would probably expect there would be some decline overall.

DR. DOMANSKI: I don't think you can use historical controls at all on that.

CHAIRPERSON CURTIS: No, I'm just saying, in terms--well, let's--

DR. DOMANSKI: But let me address--

CHAIRPERSON CURTIS: May I finish? What I was saying is that if you have a group of patients and you--were not in a trial and you had a year's worth of therapy, there might be some decline. We don't know what that is because nobody's done that. So if you take this trial and you measure patients at the beginning and at the end of the trial and you saw there was a 5 percent decline in ejection fraction, maybe that's better than it would have been. You know, you have nothing to compare it to.

So then I don't know--you know, we could measure it, but I don't know how--I mean, if it were the same or improved, that would be great. But the problem you could run into is if there's some decline, is that bad or better

than it would have been? And we don't know the answer to that.

DR. DOMANSKI: But the short-time argument doesn't wash because what you're going to have is over time the different groups are going to be switching over to other therapies over the course of, you know, a series of stints of time. And as a result, at the end of the year or whatever, you're going to be able to look at whether the group had more infarcts on therapy or off. So, I mean, you can do that. You can do that.

Kent, I mean, do you see a statistical problem?

DR. BAILEY: You know, I guess it's just an issue of logistics, but, clearly, if you only have one measurement at the end of the year and you have this confounding of different treatments, then all you can say is descriptively what happened to the whole group. You can't say anything about treatment. The only chance you have to say anything about treatment is if you measure it correlating with the treatment.

CHAIRPERSON CURTIS: Well, you know, but, again, there's a distinction between safety and efficacy. Are you saying that from a safety endpoint or an efficacy endpoint?

DR. BAILEY: Safety.

CHAIRPERSON CURTIS: Safety. Okay. Well, then--and, I mean, I think we're all kind of coming at the same

thing from different angles, but you can't measure it beginning at the end--

DR. BAILEY: Right. If you go the parallel design, that would be an argument--if you were really interested in this and you only want to measure it once, then you have to do the randomized parallel.

DR. VETROVEC: There are a couple ways around this. It seems to me one of the issues here is--Jeff is right. These people aren't dropping like flies based on the information we have, so the long-term outcome differences may be fairly subtle, and I think what we're trying to look for are surrogates which might predict a concern that would warrant better long-term follow-up if we found concerns. One of them would be the exercise test results and whether or not an exercise duration is improved with ischemia also being improved or not. And I think that would be one concern.

A second one is this left ventricular function. You might simplify it, even though you got multiple stages, to look at the time frame of control, which would be one fixed period, versus the period of highest dose that the patient was treated at if you have several doses, assuming that the highest treatment dose would be the one that would give you the greatest effect and, therefore, you might miss a silent infarction in that group. That's one way to maybe

simplify it.

The third thing that I would ask is about heart rate variability. Heart rate variability is a measure that tends to suggest adverse outcome, and this would be a very easy parameter to measure. And, again, if it's markedly changed relative to pacing or to stimulation in adverse form, that again might be a factor that would make one concerned about long-term effects.

CHAIRPERSON CURTIS: Are you satisfied with that? Okay. If there are no other comments about the safety issues here, I'd like to end the discussion about the spinal cord stimulation so we can move on to the second topic, which is clinical assessment of rate-adaptive pacemakers. We'll have the public commentary first.

MR. MIANULLI: Good morning. First of all, I'd like to thank the organizer of this panel for giving us the opportunity to comment on this topic. My name is Marcus Mianulli, and I am currently working in the therapy development group at Medtronic where I design and conduct post-market outcomes research studies. Prior to joining Medtronic three years ago, I was the technical director of the exercise physiology laboratory at the University of Minnesota for 17 years, and in that capacity, I really focused my research in two areas: one, to discern the normal physiology of daily heart rate behavior, and also on

the characterization of and performance and evaluation of rate-adaptive pacing devices, much of it in collaboration with David Bendit (ph). I still hold an adjunct position at the university, where I do teach a little bit.

We believe that the indications for pacing are very well understood. There have been numerous guidelines and educational pieces and references that have been developed by the American Heart Association and ACC, by HCFA, by NASPE, and by the FDA. Thus, the target population for this therapy is very well known to clinicians. More specifically, the FDA does have a labeling template that recommends indications and contraindications, and to a great extent, industry has adopted these recommendations.

The clinical benefit of rate response in our opinion has been well established. The rate-responsive devices have been used and exhaustively studies for over 14 years both formally in the scientific community and also informally by practicing clinicians in probably now several hundred thousand patients. Thus, the current sensor technology is a mature technology that clinicians are comfortable with.

The clinical benefit of rate response is well established and accepted by clinicians, by professional organizations, by the FDA, and by device manufacturers, and continued use does support this benefit. Therefore, it's

our contention that there is no need to reprove the benefit of rate-responsive pacing. An analogy that was relayed to me by a clinician recently was that we don't any longer need to reprove the benefit of pacing in a severely bradycardic patient to prevent syncope or pre-syncope.

The evidence required to improve rate-responsive devices we believe is really dependent on the desired claims, to echo a comment made by one of the panel members previously, and these can be stratified into two arenas: the required claim, in other words, if the device is, in fact, rate-responsive; and then, also, additional claims that may be made, and these would then be specific to each manufacturer and to each claim.

The basic question boils down to: What is rate response related to this first claim, the required claim? And one simplistic model would be that rate response is increased pacing in response to increased exercise demand which, with current devices is tracked by parameters such as activity, minute ventilation, or QT changes. And then, secondly, how then is rate response best evaluated? In line with the FDA's stance that methods should be congruent with least burdensome approach and should rely on non-clinical testing when possible, we believe that this question can be addressed by further stratification related to existing technologies versus new technologies.

With regard to existing technologies, once again, this has been extensively studied, and the mode of action and effectiveness are very well understood by industry, by the FDA, and by physicians. In some cases, we're now in the seventh and eighth generation of these devices.

We would propose that bench testing is an acceptable surrogate to prove effectiveness with existing technologies. Thus, it's not necessary to implant a device to understand its performance. In a bench model surrogate, this type of methodology can actually be more controlled and offer a greater variety of inputs versus in vivo or even strap-on testing. This method would allow comparison to approve device performance under similar bench conditions. And, furthermore, we believe the combinations of approved sensor technologies can also be evaluated in this manner.

This methodology can adequately address questions of sensitivity, of specificity, and even of proportionality of rate response, and thus can address the issues of effectiveness and safety.

With regards to new technology, certainly human evaluation is warranted when no acceptable bench surrogate is available. Now, clinical models can be very, very challenging, as I'm sure all of you are well aware. In this particular situation, there are so many variables that need to be controlled, not the least of which is the degree of

chronotropic incompetence in the patient, and even the form of chronotropic incompetence, which can be quite variable even in the same patient. Then also the wide array of concomitant medical conditions that the patients may, in fact, also have.

Given this, we believe that a reasonable model is the Wilkoff model, and for those on the panel that may not be familiar with this model, it basically describes a linear relationship between heart rate and increasing work, as described by metabolic response.

We believe that this is a beneficial approach in that it's not necessary to have entirely chronotropically incompetent patients because it is possible to look at the sensor-indicated rate of the device during the exercise test, even in situations where the patient's own intrinsic activity may be supporting their exercise for any portion of the exercise test. Thus, it does not require that you limit this to only chronotropically incompetent patients, and, in fact, this model has been used by the FDA and by industry for the last two-plus years.

This certainly would be least burdensome for the patients in that they only need to have one exercise test and also for the physician and certainly could result in a fast cycle time.

Clearly, however, additional claims that may be

made would require more complex study designs, and these would be specific to the claims that are, in fact, pursued.

In conclusion, then, it's our belief that rate-response technology has been evaluated extensively and is well accepted clinically, and that the least burdensome approach would be best stratified based on whether it is an existing technology, in which case a bench model surrogate is appropriate, versus new technology, in which case the Wilkoff model has been shown to be efficacious and to, in fact, predict response during the patient's activities of daily living.

And then, finally, the additional claims that may be made should drive specific study designs related to those claims.

Thank you.

CHAIRPERSON CURTIS: Any questions from the panel?

[No response.]

CHAIRPERSON CURTIS: Thank you. Let's go on to the FDA presentation.

MS. MOYNAHAN: Good morning. My name is Megan Moynahan. I'm a biomedical engineer in the Pacing and Electrophysiology Devices Branch. The FDA is seeking the panel's input on clinical assessment of rate-adaptive pacemakers. Our goal is to have you discuss the advantages and disadvantages of various study design options for these

devices. Like the other devices being discussed today, rate-adaptive pacemakers may have qualities that lend themselves to certain study designs, choice of endpoints, duration of follow-up, and so on.

My brief presentation will include a discussion of the various means that have been established to increase ventricular rate, an outline of methods used to evaluate the performance of rate adaption, both in terms of effectiveness and clinical benefit, and I'll conclude by introducing the questions to the panel.

In the late 1970s and early 1980s, the technologies of pacemakers grew to the point that devices could incorporate means to increase ventricular rate. The first such devices were the universal DDD pacemakers. These devices allowed patients having competent sinus nodes, but lacking AV conduction, to have their ventricles paced at a rate governed by sinus activity or atrial tracking. However, patients with incompetent sinus activity, for example, sinus bradycardia, or undesirable atrial activity, for example, atrial flutter or fibrillation, were unable to fully utilize DDD pacing. The next advance in pacing was the development of sensor-mediated rate adaption. These devices include sensors that are designed to monitor a parameter, which is correlated with changes in a patient's need for increases or decreases in heart rate. Thus,

patients receiving these devices were able to have chronotropic response restored in their ventricles.

For the purpose of this discussion, it's helpful to consider the definition of "sensor" as a combination of the transducer, which measures some parameter indicative of a patient's need for increased heart rate, and the algorithm, which relates the measured parameter to the appropriate target heart rate.

Various types of transducers include activity sensors, accelerometers, central venous temperature, minute ventilation, and others.

In evaluating the performance of rate adaption, it is important to consider both the effectiveness of the sensor and the clinical utility of the rate adaption on the patient. These will be described in more detail in the next few slides.

When we speak of evaluating the effectiveness of rate adaption, we mean that the sensor provides rate changes that are appropriate and proportionate to changes in patient activity.

By using a standard methodology, patients with rate-adaptive pacemakers can be evaluated in comparison to a normal historical control. One technique to do this derives from the work of Wilkoff, who established the normative values for patients undergoing the Chronotropic Assessment

Exercise Protocol, or CAEP. Using these data, Kay normalized the curve for heart rate versus workload and determined that a normal response would be one in which the slope was unity.

In Question 1, you will be asked to consider this method of analysis as a possible primary endpoint for evaluating the rate-adaptive feature of pacemakers and to discuss its advantages and disadvantages. You will also be asked to discuss what a clinically meaningful response would be.

When we speak of evaluating the clinical benefit of rate adaption, we mean that the sensor provides a measurable change in a clinically relevant parameter.

Parameters that have been studied and reported in the literature include time to peak heart rate, cardiac output, oxygen dynamics, exercise duration, anaerobic threshold, symptomatology, and quality of life.

In the second part of Question 1, you will be asked to discuss the advantages and disadvantages of these parameters as primary endpoints, and what you would consider to be a clinically meaningful change. In addition, you will be asked to consider the impact of these endpoints on study duration.

Because the rate-adaptive feature can be programmed on or off, investigators have favored crossover

study designs to evaluate these devices. However, other study designs may be possible, including a randomized controlled study, a single-arm comparison to a historical control, such as the CAEP, and possibly others.

In Question 2, you will be asked to discuss the advantages and disadvantages of these study designs. You will also be asked to consider how confounding variables may impact the overall study in Question 3.

I'd like to turn the discussion over to the panel. For the benefit of the audience, I'm going to read the questions.

Rate adaption has generally been associated with improvements in cardiac output, exercise tolerance, and quality of life for some patients. In addition, standardized exercise protocols relating heart rate to an age-predicted norm have been valuable as surrogate endpoints in characterizing the performance of these systems. Please discuss the advantages and disadvantages of these as primary endpoints for the study of rate-adaptive pacing.

What would be a clinically meaningful response for each of these endpoints?

For each of the endpoints, please discuss the follow-up duration necessary to capture a clinically meaningful change.

And what secondary endpoints would be important to

collect to fully characterize the effect of rate-adaptive pacing?

Question 2 asks: Please discuss the advantages and disadvantages of the following study designs in terms of their ability to evaluate the performance of the rate-adaptive feature of pacemakers: the randomized controlled study, the crossover study, a single-arm historical study, or some other.

Question 3 asks: Given the numerous types of indications for cardiac pacing and customization of the device for each patient, the potential for confounding variables in pacing trials exists.

Please discuss which confounding clinical variables, such as the impact of physician programming, could significantly impact the design and/or outcome of these trials. And please provide any suggestions regarding clinical study design and data analysis for these trials.

I'd like to turn the discussion over to the panel, and I'm available to answer any questions that you may have.

CHAIRPERSON CURTIS: Thank you.

DR. BRINKER: Can I--excuse me. What is the genesis of this issue? Quite frankly, I'm old enough to have been on the panel when we gave a rate-adaptive approval for the devices based on anaerobic threshold of benefits, and it seems to me a well-established principle that rate

adaptation in patients who need it is a valuable adjunct. So that the issue of rate adaptation is, I think, a done deal in terms of whether it's effective or not. So maybe you could tell me what the issue is, actually, that you're trying to get at.

MR. DILLARD: I think there's a couple issues that we're struggling with, and I think that this is the one, as I led in my discussion this morning, that we have been dealing with for a longer period of time than, of course, the other two issues today.

One thing that continues to come up in terms of study designs for newer types of products, which is not reinventing the wheel, which I think is your issue that you're bringing up, but it is established in some patient populations, it is established for particular groups of individuals that we understand sort of their clinical etiology and symptomatology, but there are newer patient populations that could be on the horizon.

And so one question for you all would be: Based on what we know now today and the establishment of the technology in some patient populations, what types of trial designs and/or clinical issues with an established technology should we be focusing on if we need another clinical study for another individual patient population?

CHAIRPERSON CURTIS: What kind of patient

population are you talking about?

MR. DILLARD: Well, and I'm not sure--Mitchell, I don't know if you can add anything in terms of specifics, but--

MR. SHEIN: Mitchell Shein, FDA. I think as this time it's not necessarily an issue of patient populations. I think as people look to develop sensors further, you're talking about a finer line of increment in changes of benefit. And I think what we're looking at here, I think that I would certainly accept that the concept of rate-adaptive pacing is certainly beneficial and efficacious in patients. I think the question that gets raised is: Are the new combinations of sensors or the new sensors that may be introduced, are they in combination with the algorithms that govern that? Are they going to be able to deliver the promise of rate-responsive pacing? And I think that we're asking you now that we're looking to re-evaluate. There's new science. There's certainly a growth in the industry. Are there other ways to look at this that we should be considering other than what we've been bringing to the panel historically.

CHAIRPERSON CURTIS: I would think in general that--I think we would all agree that rate-responsive pacing helps patient who have chronotropic incompetence and that the technology is well proven. So I would think in most

cases what you're looking to prove is that the pacemaker makes the heart rate go up the way it's supposed to. We're not looking at quality of life and proving that--you know, I mean, what we're looking at is does the pacemaker do what it's supposed to do, which is increase the heart rate in a physiological way that is according to the Wilkoff and Kay models.

I think if you've got that in most cases, then you say it's a rate-responsive pacemaker. I think if there's some other claim that's being looked at, that would be different. I'm not personally all that concerned about combinations of sensors that are established as long as they increase their heart rate in the way it's supposed to. If somebody wants to claim that a combination of sensors is better than a single sensor, well, then, you may have to be looking at exercise times and quality of life or other issues like that. But if the question is does a sensor or combination of sensors works, put them on a treadmill and see if it takes the heart rate up. That's really all you need. You don't need a whole lot of other data, I don't think.

DR. BRINKER: I don't think you ought to put them on a treadmill, actually. I think that--

CHAIRPERSON CURTIS: It depends on the kind of sensor. You know, with--

DR. BRINKER: If it's an accepted sensor--

CHAIRPERSON CURTIS: Right, I agree.

DR. BRINKER: --you can model, that has been discussed, and I think these are sort of critical issues. I agree perfectly with Anne that if there's a new claim or a claim for superiority, that requires further evaluation. But this other stuff seems to me pretty accepted.

MR. DILLARD: Dr. Curtis, can I add to my second point, which was--the second issue that I think we're struggling with is just the terminology that I think you used, which is that the products are performing the way they are supposed to. And, clinically, in your judgment, what is that, "the way they're supposed to"? I mean, is there any other clinical guidance in terms of how close they need to be to the particular model situation for you to feel clinically reasonable enough that they are performing the way they are supposed to? And I think that's another issue that is embedded in these questions that I think if we could have some discussion on would be helpful to us.

DR. BAILEY: Is there a question here whether you have to evaluate it in the chronotropically incompetent person to demonstrate that it does the right thing? Or can you do it--

CHAIRPERSON CURTIS: Well, a lot of these pacemakers can tell you what the sensor indicated rate would

be, so--

DR. BAILEY: And that's accepted as telling you that it will do the right thing?

CHAIRPERSON CURTIS: Yes, because, I mean, if the patient were chronotropically incompetent, then you'd be pacing at, say, 130. If the patient's chronotropically competent and they get up to 140, the sensor could still tell you it was going to go to 130. So you can see that . So that's not so much of an issue.

MR. SHEIN: That's to some degree quite accurate, but you also have to take into consideration in the patients that are chronotropically incompetent if you want to make a further claim for the device. If you're only looking at the sensor-indicated rate and it's masked by intrinsic rate, then you don't know what effect the changes or the differences in rate might have on the patient's exercise performance?

DR. BRINKER: But those have been modeled. I mean, there's--we have data from previous studies to show that a chronotropically incompetent patient is improved, at least in terms of anaerobic threshold and exercise performance in other studies by methodologies which augment rate.

One issue, I guess, is that almost all of these sensor-driven pacemakers have means to customize sensor's

appreciation of whatever it's measuring so that you can basically change the rate responsiveness per patient. And that's a good thing because not every sensor works the same way in every patient. There are little patient-sensor interactions that should be fine-tuned. The problem is that physicians--and this is a doctor problem, not necessarily a manufacturer problem. Many times the nominal values that are achievable out of the box for sensor drive aren't the most optimal for a patient. And it depends on the physician to take the time to adjust them appropriately.

MR. SHEIN: That's absolutely correct, and this goes right to the question Mr. Dillard just raised, that in the patient in whom the device has been customized, to the extent that the device is capable, how good is good enough? How close do you have to come to the model to be an acceptable rate-responsive device? And that's one of the things that we're certainly looking for input from the panel this morning.

CHAIRPERSON CURTIS: The handout that we had from Medtronic on it was talking about new sensor technologies and mentioned actually a very specific means of programming and evaluating, programming 85 percent of the age-predicted maximum, which is 220 minus the age, maximal exercise, and then having a slope where the 95 percent confidence interval was between 0.65 and 1.35. And that says--and it says,

"Essentially this method has been FDA's guidance over the last 2 years."

Have you perceived a problem with that? Because, I mean, that seems fairly straightforward.

MR. DILLARD: Let me make a comment on that. While that has been in our guidance and it has been something that we've utilized, sometimes when we do come up with those values, perhaps the technology at the time when we develop the guidance fit within that window. Obviously, there's a change in technology, and there sometimes is a change in the perception of whether those values are still appropriate. And I think it isn't so much that we're struggling with those values. One of the questions that I've had is what's the clinical basis for those values necessary. Is there clinical reality in those numbers? And if there isn't and if there's something else that we should be looking at, I think that's one of the questions here potentially for discussion, which is are we on the right track. It's been in a guidance. Some of these things that have been out there for quite some time are what we've been using. Is it what we should still be using? Is there any other clinical guidance that based on today's technology we should be considering?

CHAIRPERSON CURTIS: Go ahead, Renee.

DR. HARTZ: Mitch, I'm confused. If you have--

you're talking about a bench model for comparing sensors. Really you're looking at new sensors and are we going to accept new sensors. Can you in an engineering sense take a patient who's got pacing electrodes--just say a post-op heart has two atrial and two ventricular pacing electrodes. Can you mimic the sensor conditions external to the patient without implanting the device under the skin? Can you mimic whatever you want for that sensor?

MR. SHEIN: Personally, I'm not confident of that. I think that Medtronic in their discussion earlier suggested that they believe a bench study could be done with that. I hold out--and I guess I'm a little bit more conservative personally--that there are variables that you can't control for on a bench study no matter how much you throw at the device, and perhaps that may have a play on how the device interacts with the patient. Therefore, some clinical proof of concept to a degree would be appropriate. But I don't know from where--

DR. BRINKER: Are talking about new sensors or commonly accepted sensors that are placed in just a different cam?

MR. SHEIN: That's a two-part question, actually, Jeff, Dr. Brinker. Is it a new sensor? Well, is it a new sensor to an individual manufacturer and have they shown that they can take that technology and incorporate it within

an appropriate algorithm? Or is it a new--something that's being imported from another area, for example, some of the sensors that might be used in rate-responsive pacing if you wanted to take those out of that area and apply them perhaps to congestive heart failure, some of the pressure sensors. You know, does the company have the technology and have they shown that what they're using in the technology is appropriate and can they import it to another system? Or is it something that the company is coming out with de novo on their own?

DR. BRINKER: See, I think so much of this may be a case-by-case issue that it may be very difficult. In the last scenario, you just suggested that, well, maybe there is a group of heart failure patients that are going to get paced now and we're going to try to--there may be some sensors that are inappropriate in these patients for one reason or another. But it's unlikely that all of them will be, and for the general population, I think, the standard sensors are quite good. The issue about clinical adjustment of these is problematic in some circumstances because it may take time and effort to program them optimally, and this is a patient/device-specific issue. I think any of these devices can increase the rate with increased metabolic demand, which is the critical issue.

So I'm not--I would say that for specific

indications, perhaps pacing and heart failure, there may be more concern about specific sensors, and that may have to be looked at. But I would hate to see sort of a retrospective desire now to relook at all the sensor-driven pacemakers to see whether they, in fact, can meet any new clinical guidelines or new--

MR. SHEIN: I didn't mean to suggest using them in a new population. What I was trying to--what I was saying there is if you wanted to take a sensor that perhaps a manufacturer such as (?) had, and they wanted to move it to a different cam for a different indication, then we would have a higher degree of confidence that they could make and they could implement the use of that sensor, that they knew the data, the output of the sensor and how it would be transcribed by their algorithm, as opposed to when Teletronics first introduced the MV sensor, that other companies went and for the first time in other companies, such as Medtronic or (?) , introduced a minute ventilation sensor, would that be a well-known, well-described sensor at that point?

DR. BRINKER: But, I mean, see, this kind of issue is, it seems to me, not a panel issue but an FDA regulatory issue.

MR. DILLARD: Jim Dillard. Let me just add something here. Maybe I can refocus this. We don't

disagree with you that there are many things here that are FDA issues. I think our attempt here today was to see whether or not 10, 14 years down the line, based on what we've been doing to assess this particular technology, whether there was anything additional from your clinical vantage point that we should be considering in terms of taking a look at assessment of the technology. And it wasn't our intention to come in and have you struggle with this, or the way we currently are, but if there was anything additional that we should be thinking about to get any input that you have based on what you know today. And it may well not be the case, but, you know, what I'd like to do--and perhaps maybe one of the focuses could be could we walk through perhaps the question. There may not be anything to add. There may be just what you're doing is currently fine, we don't anticipate any changes, and that's an okay answer. But at least maybe we can have some focus into the issue.

DR. HARTZ: What I was trying to get at earlier is the industry could figure out a way to mimic the conditions of each sensor. There's a stable full of patients who as paid volunteers could answer these questions. You could use five or six sensors on an individual patient. That would be a patient two weeks after bypass surgery, there's no problem leaving temporary wires on a patient for two weeks. I don't know if you can do that, but that certainly is a captive

audience. It would be a wonderful study to do, and patients would be coming back, you'd know if they were okay clinically at, say, two weeks after surgery. And is that a model that you might want to consider using in the future for studying new sensors? And can you mimic the conditions externally?

CHAIRPERSON CURTIS: I think that's probably something that can't be done because, you know, over the years certain kinds of sensors that have been brought up, like body temperature, you have to record body temperature internally, so you can't mimic that from outside. There are certain other measurements that are made that either require special leads that are transvenous leads or require some measurement that's made that you can't mimic from outside of the body.

Activity to some extent can be, and people have strapped on--

DR. HARTZ: The minute ventilation.

CHAIRPERSON CURTIS: Yes, that you can do that from outside. But I think in most cases you probably are not going to be able to do it that way.

I'll be happy to go to the questions now. I'd just make one other comment now. If these pacemakers had one slope to them and that was it and the patient got it, I think you'd have an issue about, gee, you know, is this the

right one. But all of them are adjustable. And the bottom line is that the pace--if a patient has a fixed heart rate of 70 versus a heart rate that changes with their exertion, it makes a huge difference. And it doesn't really matter a whole lot if, you know, they get to 110 or 120. You can always fine-tune it later on. But effect, you know, benefit--there was a huge benefit to that patient and the fine-tuning is something we can do. We don't have to match the slope of the Wilkoff model exactly. I think you have to get within that range. But as long as you do and as long as the pacemaker's programmable, we can work with it.

Go ahead, Tony.

DR. SIMMONS: I think the other thing is--it's unfortunate in some respects. I think all of us would like to think that, you know, one sensor or one programming or one particular individual can be optimized. But it hasn't worked out to be that way. Unfortunately, if they get a rate response, they're better than not having a rate response. But it doesn't seem like there is an optimal rate response. Certainly even in the panel pack, Neil Kay's article where he just had the heart rate jump up to its maximum rate sensor a few seconds after, those patients got tremendous benefit.

So, you know, there is a clinical benefit, but trying to sort out gradations of clinical benefit have not

been very productive. It's frustrating but true, I'm afraid.

CHAIRPERSON CURTIS: Yes. All right. Let's look at Number 1. Looking at cardiac output, exercise tolerance, quality of life, other endpoints for the studies. I'm not sure I really think that much has to be done differently from the arguments made about very well-established sensors like the piezoelectric crystals and that sort of thing could be bench tested and that new technologies require a treadmill test. But the treadmill test, in showing that the heart rate increases is what we need, I don't think you have to revisit quality of life or any other issues.

Does anybody else want to make some comments on that?

DR. VETROVEC: The only question I have is that because many of these patients have bad ischemic disease, is there a point at which you run the rate up and theoretically the cardiac output, all those good things happen, but the patient is now limited because of angina, and have you really changed the limitation--or the cause of the limitation, but you really haven't changed the functional performance.

DR. BRINKER: Let's again look at what we're doing. This is a device that is programmable by the physician to tailor to the patient. You can't--I mean, you

can't design a device specifically for the patient with angina who might need some rate adaptation. And I think that the--I personally think that a mimicking of the--using Wilkoff and Kay models, are quite adequate to show what the sensor can do in the typical issue involving sensor-driven pacemakers.

There may be other indications that are suggesting a cardiac--that there might be a benefit in sensor-driven pacing beyond that which one would attribute to the chronotropic response, for instance, in heart failure. In that case, I think that you would need the appropriate clinical trial to show that there is a benefit for driving up rate, for instance.

Also, there may be other algorithms tied to the sensor-indicated rate that might need evaluation in some way, for instance, changes in AV interval or tracking in the past that may have needed some evaluation. But I think even now those can be modeled appropriately at the bench top.

So I think unless we're dealing with something new or a--I don't think we have to re-establish that increasing rate for the usual purposes is clinically beneficial. What we do have to establish is whether the device does, in fact, increase rate as advertised, and I think that for the--unless there's something really new about the sensor that might be not imitatable in the bench, on the bench, that a

clinical trial is necessary.

CHAIRPERSON CURTIS: Do you have any other concerns about Number 1? Number 2, clinical trial designs here. Any comments?

DR. BRINKER: Well, again, if you're using a new sensor, I think that the clinical trial would be pretty much to show that it increased rate, not that it increased patient benefit.

CHAIRPERSON CURTIS: Right. So you basically would put it in and put them on a treadmill and see if the heart rate goes up. I don't think you need anything more than that.

All right. Number 3, potential for confounding variables. I think we were getting into that a little bit already, that you have to fine-tune these things for the patient. We'll do that off and on on any individual patient we put these things in forever. So certainly there are impacts of physician programming. Actually, more often than not, physicians don't reprogram these things as often as they probably should. But, again, you know, if you turn on the rate-responsive feature and even using nominal values, the majority of the patients you'll be in pretty good shape with. And since we're not talking about big extended clinical trials, then issues about physician reprogramming I don't think really come up.

DR. DOMANSKI: I think that's right. I think I agree with what the panel said. If you were going to design something, just kind of a clinical trial's point, the way you'd probably do it is, you know, if you were going to do a big randomized trial, totally unnecessary, I entirely agree with more or less the Medtronic presentation at the beginning.

But having said that, if you were going to do it, what you'd do is you'd randomize people to best possible physician input, programming versus, you know, no rate response, I suppose, and then you'd have yourself a trial. And that's the way you'd take into account the fact that there are variations in programming.

DR. BAILEY: What if you were trying to make a claim of superiority between a new technology?

DR. DOMANSKI: Then you could do exactly that. You'd randomize to old technology, optimally programmed as best the doctors could, versus new technology optimally programmed, and pick an endpoint of your choice and go at it.

DR. VETROVEC: You might add to it guidelines for how the physician optimally programs it.

DR. DOMANSKI: Always in the ops manual.

CHAIRPERSON CURTIS: Any other comments?

[No response.]

CHAIRPERSON CURTIS: Are there any other final public comments anyone wants to make on either of the first two issues we discussed this morning?

[No response.]

CHAIRPERSON CURTIS: Okay. If not, then I'd like to announce to the panel that in the back of the restaurant there's a table set aside for us for lunch. We will break for lunch now and reconvene at 1:00 p.m.

[Luncheon recess.]

AFTERNOON SESSION

[1:05 p.m.]

CHAIRPERSON CURTIS: The topic for this afternoon is clinical trial designs for treatment of atrial fibrillation. We'll have the public discussion first, and we have a representative from Medtronic who's requested time.

DR. GOLD: Good afternoon. I'm Michael Gold. I'm from the University of Maryland, and I'm a clinical cardiologist, clinical electrophysiologist. I've been asked by Medtronic to speak on this topic. I received support for coming down here, reimbursement for coming down from my expenses, and also have received honorarium for speaking as well as clinical support for participation in clinical trials, but I have no financial or equity interest in any of the products or in the company being represented today.

I've been asked to speak about the issue of device therapy for treatment of atrial fibrillation. I will not be speaking about ablation but simply about other types of devices. And to start out, I will only be speaking about devices used for the sole indication of atrial fibrillation and will not be talking about those devices that are used as adjunctive therapy for patients who already need some device for the treatment of atrial fibrillation. So my discussions will be limited to the AF-only population, in which I think

it's obviously necessary to demonstrate both the safety and efficacy of this therapy in the indicated patient populations.

There's also the issue of patients who have other indications for devices, either significant bradycardia, such as sick sinus syndrome, or significant tachycardia, such as ventricular tachycardia or fibrillation, who are already receiving devices for those. The issue of treatment strategies for atrial fibrillation in those devices are somewhat different. The safety and efficacy of the primary indication has already been proven, and, therefore, I think the addition of therapies for atrial tachyarrhythmias require that there's no incremental safety risk for those patients and that the algorithms to treat the atrial arrhythmias perform as desired.

As I mentioned, I'll now be restricting my discussions to device therapy for atrial fibrillation. I think it's somewhat unique or different in that the specific study designs that we've been asked to comment on are really variable depending on the specific questions. So I think the therapy really guides the direction that one goes, and whether that therapy is designed for termination of arrhythmias or prevention of arrhythmias will then determine and drive the clinical question. The clinical question then drives the study endpoints, and that finally determines the

study design, which as I'll mention in the next couple slides can be very variable depending on what type of therapy we're looking at.

The therapy types can be grouped largely into two types: those for termination of arrhythmias, and they can then further be subdivided. There is early delivery of therapy to try to terminate atrial tachyarrhythmias, which is typically painless pacing therapy. Because this is painless, it's delivered very soon after the initiation of therapy. Because there is often spontaneous terminations of these arrhythmias, the design of these types of evaluations are different than the design of late delivery of therapy. And the late delivery of therapy typically in this field is shock therapy, which causes brief but painful shocks to the patient, and because the spontaneous termination of arrhythmia within several seconds after an arrhythmia has been persisting for hours and hours is very unlikely, again, the design of these types of studies are different.

And the second main type of therapy is the prevention therapies, those designed to try to prevent the initiation of atrial tachycardia and atrial fibrillation. These again tend to be painless pacing therapy.

What's shown on this slide are some data of episodes of durations of atrial tachyarrhythmias from patients with an implanted pacemaker, the AT-500 device, and

I think this helps illustrate some of the problems with designing trials for the evaluation of termination therapies. A vast majority of these episodes lasted less than ten minutes, yet the pacing therapies that are often used can have durations of therapy for minutes on end. Therefore, one gets the false impression of a much higher efficacy rate if we simply give two to three minutes or five minutes of pacing and look at how often the arrhythmia has terminated. I think obviously this is a critical aspect in terms of designing trials to assess whether our therapies are working or not.

In terms of termination therapy for atrial tachyarrhythmias, I think the clinical question is: Are termination therapies safe and effective in the indicated patient populations? And there are several endpoints that can be looked at. In terms of safety endpoints, the most common safety endpoint to look at is adverse events, and adverse events can be looked at in many ways, but usually prospectively looking at these devices.

In terms of efficacy, I think there's a difference in terms of how we evaluate efficacy depending on the therapy that's being given. For early pacing therapy, the most relevant efficacy is some measure of burden reduction. Again, because we can't reliably assess how frequently the arrhythmias are actually being terminated by therapy since

these therapies are often self-limiting, looking at the overall reduction in the amount of the total time of an arrhythmia is probably the most appropriate endpoint to use to evaluate these sorts of pacing strategies.

In contrast, for late delivery or shock therapy, the percent termination of these arrhythmias are very appropriate since spontaneous terminations are an extremely rare event when we're looking at delivering shock for arrhythmias that have been present for many hours.

With regard to specific study designs, therefore, for the early delivery of therapy for pacing type of therapy, I think either a crossover or a randomized design is necessary to actually establish a reduction in arrhythmia burden with that pacing algorithm compared to that pacing algorithm not being turned on. I can see no other way of being able to assess this.

In contrast, for late delivery and shock therapy, since the spontaneous reversion of these arrhythmias are next to nil, a single-arm evaluation evaluating the efficacy of shocks appears to be appropriate.

In terms of what's been considered acceptable endpoints for these types of studies, for safety there's a very large literature on the rates of adverse events with other types of devices, either pacemakers or defibrillators are very well described. There are some potential unique

adverse events that can develop with these types of therapies, such as proarrhythmia due to shocks or pacing, although I think at this point it's quite well established that there's very low incidence of that with properly used devices.

With regard to efficacy of termination, for early delivery or pacing therapy, efficacy reductions of 25 to 35 percent reduction in burden of arrhythmias seems appropriate based on the literature, while for late delivery or shock therapy probably a minimum of 70 percent success rate for terminating arrhythmias would be appropriate. These numbers, the 70 percent is a little bit lower than we're used to for implantable ventricular defibrillators because of the problem of early recurrence of atrial fibrillation. Many arrhythmias, atrial fibrillation, a certain proportion are successfully terminated, but then reinitiate within seconds or less after termination. So the goal of reaching 90 to 100 percent, at least at this point, is probably not attainable with our present understanding of arrhythmia reinitiation with atrial arrhythmias.

With regard to the problem of prevention, the clinical question here is a preventable algorithm safe and effective, again, in the indicated patient population with atrial tachyarrhythmias. With regard to the study endpoints, the safety here again is a measurement or

monitoring of adverse events in this population, and the efficacy is probably slightly different in terms of how it can or should be measured.

Since preventative algorithms are thought or at least our best understanding at this point are going to prevent the initiation of arrhythmias and not the duration of arrhythmias, it would be simplest and easiest to simply measure arrhythmia frequency to see whether the frequency of arrhythmias are reduced with the preventative algorithm. A second endpoint obviously should be the measurement of arrhythmia burden, with the expectation that burden is going to change in parallel with changes in frequency of arrhythmias, assuming that prevention prevents the all or nothing arrhythmia and then the duration of arrhythmia is controlled by whatever factors control a duration of those arrhythmias.

In terms of the study design, again, for prevention algorithms, I think properly controlled studies are necessary, which will require either a crossover or randomized design. I think we've already touched on the topics earlier this morning with regard to crossover patients, requiring less patients, potentially having more power of randomized design, getting around the problem with having separate groups, so we get around the problem of any carryover effects of any of the preceding therapy.

With regard to an acceptable threshold or these endpoints, for safety, once again, there's a very large literature on adverse events that are seen in these similar types of devices that can be used for controls, and in terms of efficacy of prevention therapy, once again, a 25 to 35 percent reduction in the frequency of atrial tachy-arrhythmias would be consistent with what's been in the literature.

So, in conclusion, I think for pacing therapy, as an endpoint of burden reduction in episodes of atrial tachyarrhythmias is probably the most appropriate endpoint in this population. And the study design should probably be either a crossover or randomized controlled design. With regard to shock therapy, which occurs much later with more sustained arrhythmias, the appropriate endpoint appears to be the percent termination of arrhythmias with that specific therapy, and a single-arm study seems sufficient to be able to analyze the efficacy of this therapy.

Then, finally, with regard to preventative algorithms, which tend to be painless, the endpoint there would be a decrease in the frequency of atrial tachyarrhythmias with, once again, the study design being either crossover or randomization in a controlled study design.

Thank you.

CHAIRPERSON CURTIS: Any questions?

DR. BRINKER: I have one, Mike. Is the AF burden, the reduction of some X arbitrary percentage, you don't--you measure efficacy, you propose measuring efficacy simply on reduction of time in AF, and we have an arbitrary amount that would seem on first blush reasonable to achieve. There is an omission of any clinical impact of reducing this incidence or time in AF by 25 or 30 percent or 40 percent.

Would you propose, number one, that a reduction of this level, this minimal level, would make a symptomatic change in the patient's quality of life? Or would you suggest that you might not--you might be able not to treat with anticoagulants or antiplatelet agents in these people given that much of reduction, but not complete suppression? What would be a clinical relevant endpoint to that?

DR. GOLD: Good questions, and difficult questions, obviously, to answer. I'll start with the second one first because I think that's a little bit easier in my own mind.

I am unaware of any data to suggest that any treatment to prevent atrial fibrillation prevents embolic complications. The affirm study is going on with follow-up, but it's unclear to me at this point that even if we think we're preventing a-fib with antiarrhythmic drugs that we are necessarily preventing embolic complications. So I would

not at this point tie any of therapies or efficacy to a necessary reduction in embolic events, and in my own practice, reducing AF 20 percent, 30 percent, 80 percent, 90 percent, I don't know that that prevents or reduces the risk of strokes or anything else embolic. So I treat them all with the one drug I know prevents those problems in those patients, which is warfarin at this point in anyone who can take it.

With regard to your first question, which is, I think, the more difficult one in terms of the benefit to the patient, we certainly know that atrial fibrillation is associated with decreased exercise capacity, with symptoms of palpitations, with multiple other issues that bother the patient. The issue of quality of life is a very murky and difficult one often to use in this sort of venue, but, clearly, the assumption there is that one would require a significant amount of reduction in their time in atrial fibrillation to make the patients function better or feel better.

DR. BRINKER: Well, I think that that's sort of the key to the question. If you can--since, as you suggested on your chart of the durations of these events, most of them are exceedingly short and probably not manifest by very much in the way of symptomatic encumbrance to the patient. Maybe they are. But if you were to judge efficacy

solely of the device, clinical efficacy, on the ability to reduce the total amount of time by 35 percent, let's say, do you think that should be a stand-alone--that that's good enough for a stand-alone demonstration of clinical efficacy? Or would you want to tie that in with some kind of clinical measure?

DR. GOLD: Again, I think for me it's easy to quantify a reduction in burden, relatively easy. There are problems with that as well. But reducing the amount of atrial fibrillation I think is easy to quantify. Requiring the quality-of-life issues or some other--exercise duration or some other issue for the patient certainly is logical and makes sense. I just have problems with trying to figure out what that quality of life would be and what those issues would be. So--

DR. BRINKER: Well, let me turn the question around. I don't know--obviously, reduction in AF time is quantifiable. But if it turned out that the patient didn't appreciate any difference--and I don't think you've shown me any evidence that there is any long-term benefit in and of itself of a 35 percent reduction in AF time, are we following a lab value that we can influence but may not have any clinical extension? I mean, it would be nice to say, well, I've reduced the AF by 35 percent, but the patient's no different, and I am exposing him to a form of therapy

that is somewhat invasive and has a few potential untoward events associated with it, but not many, I will admit. But if we're not gaining him anything that he can perceive or that we as clinicians can perceive to be in his long-term benefit, are we doing him a service simply by reducing the burden by that much?

DR. GOLD: And, again, most of it--most of my argument is extrapolation from other things we know about atrial fibrillation from studies in heart failure patients which showed that if we reduce atrial fibrillation with a variety of drugs, that that's a group of patients who are less likely to be hospitalized, less likely to die, that survival is better in patients without atrial fibrillation or less measurable atrial fibrillation than those with atrial fibrillation. Patients with less measurable atrial fibrillation have greater exercise capacity and other things.

In the past, we did not have the tools to be able to measure arrhythmia burden, to be able to know. Most studies, patients come in on weekly or whatever--a biweekly basis and have a random assessment of their rhythm at that point. So it is very hard now that we have these tools and have a much better way of being able to quantify that, to compare that with all the other studies, but I think the literature is fairly clear, in my mind, at least, that those

patients who have less atrial fibrillation by whatever intervention are functionally better. And, therefore, if we have a device that can reduce and give us less atrial fibrillation without significant risks to it, that those patients should do better.

But to go on and repeat a study similar to Diamond or a subanalysis of CHF stat or some of the other studies which are shown there, if we look once a month or once every three months at their rhythm and if they're in a-fib, they don't walk as far on a treadmill or, you know, don't live as long or end up more times in the hospital, my assumption is that that literature is fairly well developed to suggest that keeping people out of atrial fibrillation is better for their functional status. And whether this is the appropriate threshold for that or not, I don't know. But I'm not sure that we'd need to repeat all of that literature once again in a device that's been shown in many other settings to be beneficial to patients maintaining sinus rhythm.

DR. DOMANSKI: You know, we're actually doing the affirm trial, and I've spent a fair amount of time with that group, that a-fib group, and also with the folks at NASPE. And, you know, the business of the atrial fibrillation is a tricky one because there are innovative therapies that are coming online. It seems clear at this point that the really

hard endpoints, obviously mortality, the size of a trial necessary to demonstrate a mortality difference based on these devices is--you know, it's not feasible. It would be ridiculously large.

Further, with the modern approach to anti-coagulation, trying to show a difference in embolic events would be similarly not a reasonable undertaking.

One can certainly use quality of life as something you can randomize and actually ascertain an endpoint. It's a little bit softer endpoint, but in the end it's what we make many of our decisions in atrial fibrillation based upon, actually, when we do it clinically. So I think that those are reasonable--that is a reasonable clinical endpoint to look at with these devices. And, of course, the other thing is just plain looking at the a-fib.

I would tend to reject the mortality argument relative to a-fib. It's true in all of the databases. And we've done this with our multi-analysis. Almost anywhere you look atrial fibrillation is an independent predictor of mortality in patients. But it probably--it more likely represents a subtle integrator of how sick a heart is than something that of itself causes the mortality. So that just keeping people out of it may or may not have anything to do with it--may or may not.

DR. GOLD: I agree. It's a difficult issue, but

the groups at least that--the few studies that have looked at the patients on drugs who ended up in sinus rhythm did better whether--the reason that they did better or went into sinus rhythm is because they were less sick is always arguable. They're not randomized studies.

DR. DOMANSKI: So I guess the end of my own sort of soliloquy on the subject is I think there is a clinical endpoint one can look at, and I think that's quality of life. I think it's also fair to judge these--I want to render the opinion. I think it's reasonable to use prevention of atrial fibrillation or keeping people out of atrial fibrillation, reducing the burden--you know, we've looked at time to first recurrence, burden, and so forth. We can talk about specifically which endpoint. But a device that keeps people out of atrial fibrillation or rapidly gets them out of it may, in fact, be a reasonable endpoint for FDA to consider as well as QOL.

DR. VETROVEC: I have a question. Do you know what degree of symptoms the patients experience with the defibrillator? Do you have a sense of that? Because one of the--or with the pacing, because one of the possibilities is that some of these patients that aren't aware of their atrial fibrillation will now become aware of something symptomatically.

DR. GOLD: It's a good question. The general

experience that pacing is probably painless or close to painless, when we--either preventative pacing algorithms or rapid pacing in someone who's already in tachyarrhythmia, it's very rare that patients will complain about that. It's very rare for a patient not to complain of a shock. Shock therapy is painful. We don't have any way around that at this point. And there are various ways of delivering shocks to patients, either intentionally programming it for when they're in their sleep or letting them pre-medicate themselves and activate it to give themselves shocks. Since these are not immediately life-threatening arrhythmias, there have been various approaches attempted, which is one of the reasons why I mentioned that shock therapy is normally delayed in these devices. We don't want to give immediate shocks to every episode of atrial fibrillation since 90 percent of them are going to be self-terminating, anyway, and you're probably better off minimizing the discomfort to patient by either allowing them to repair themselves or doing it at a time when they're not going to be in the middle of some action that's going to be deleterious to them to get a shock.

CHAIRPERSON CURTIS: Are there any other questions that directly relate to the presentation of Dr. Gold? Because a lot of this is going to be discussion among us about the clinical trial design.

DR. BAILEY: Well, maybe this can wait, but the problem I guess I have with the burden is that it's an average of time free of--or spent in atrial fibrillation among the different people. And it would seem that if you could actually prevent atrial fibrillation in some patients, perhaps that would have some clinical impact in terms of not having to be on anticoagulants. But if you just change it from, you know, an hour a day to half-hour a day, I'm not sure that that has the same impact.

So I would think you might want to look not at minutes in atrial fibrillation as much as the number of patients who actually have it prevented.

CHAIRPERSON CURTIS: Well, I think some of what was going on before that you were talking about, I think quality of life is essential, because if we get a printout from a patient and we go, Congratulations, you know, you've had 15 episodes not 20 and the patient doesn't feel any different, I'm not sure how great--you know, how excited they're going to be about that prospect. What we really want is the patient to come back to the clinic and say, You know, Doc, I really feel good now.

DR. BAILEY: The other question I have is--I may have missed it, but why do you not feel you could randomize patients to the shock?

DR. GOLD: I think one could randomize. I think

the efficacy of shock can be assessed by how frequently it works. Since there are essentially zero spontaneous terminations of arrhythmias over any 30-second period hours into it, if we want to know whether--the efficacy of the shock, does the shock terminate the arrhythmias, I don't think we need a control group to be able to assess that.

DR. BAILEY: How do you come up with 70 percent as the minimum--it seems to me that that figure is going to be very strongly related to the substrate of patients that you've got rather than the device per se.

DR. GOLD: I think the literature based on--there's fairly extensive medical literature now on internal atrial defibrillation with various different devices that suggests that around 70 percent or greater is the sort of success rates that can be achieved, and that the reasons we're not higher are because of the early recurrence of atrial fibrillation.

DR. BAILEY: I guess I'm suggesting that the rate is less--is not apt to be as much a property of the device as it is of the patient.

DR. GOLD: I think that's correct, that the arrhythmias--any given patient, probably whatever device one put in there, if there was an adequate shock, the patient is determining factors that we don't understand at this point, why they're going to AF or why they wouldn't.

DR. BAILEY: So then the benchmark becomes spurious.

DR. GOLD: Again, I think one--an adequate functioning device should have a success rate of a certain percentage. We certainly can put in devices that have insufficient energy or other factors or lead systems that are inefficient in which they would not be able to achieve that rate of success. I think that gives us a ceiling on our rate of success based on patient factors.

CHAIRPERSON CURTIS: Okay. Thank you. Is there any other member of the public who wanted an opportunity to speak now?

[No response.]

CHAIRPERSON CURTIS: If not, let's have the FDA presentation

DR. PORTNOY: Good afternoon. My name is Stuart Portnoy, and I'm a physician at the FDA. The afternoon session of this panel meeting, including the materials provided in your panel packs, were prepared by myself, Marian Kroen, Dina Fleischer, and Doris Terry.

Here's an overview of my presentation, which will take around five minutes.

Atrial fibrillation is the most common chronic tachycardia and the most common cardiac cause of stroke. Approximately 6 percent of the U.S. population over 60 have

atrial fibrillation, and its incidence increases with increasing age. As a result, atrial fibrillation is a significant public health concern.

Investigators are currently using a variety of medical devices in an attempt to either treat or cure atrial fibrillation. These include pacemakers, ICDs, and ablation systems. Each device intervention has its own risks and benefits. One of the reasons that we've convened this panel meeting is to ask you to discuss clinical trial design issues for each of these device types. In answering the questions, please keep in mind the potential risks and benefits of each type of medical device. FDA believes that risk/benefit considerations play an important role in discussing clinical study design issues for these AF interventions.

There currently are several studies reported in the medical literature which suggest that pacing therapies may be effective in preventing and/or treating AF through overdrive pacing and other similar pacing techniques. Likewise, the medical literature reports favorable preliminary findings regarding the clinical utility of using atrial defibrillators to treat patients with AF. Atrial defibrillators use shock therapy to terminate episodes of AF much like ventricular ICDs. Atrial defibrillators also use pacing therapies to prevent and/or terminate AF.

Finally, RF ablation systems are currently being used to create patterns of linear lesions to reproduce the surgical MAZE procedure, and most recently, investigators are treating AF by performing focal ablation of one or more pulmonary veins. Please keep in mind that while pacemakers and atrial defibrillators are designed to treat or prevent AF episodes, both linear and pulmonary vein ablation have been reported to be a potential cure for AF.

In July 1998, the Circulatory System Devices Panel met to discuss clinical trial design of linear ablation studies. Today we are broadening this discussion to include other device therapies. At the July 1998 panel meeting, the panel agreed that there did not seem to be an appropriate control for AF linear ablation studies. Therefore, they suggested that a randomized controlled clinical study might not be necessary in order to evaluate device safety and effectiveness of linear ablation for AF; rather, a single-arm study in which each patient serves as his or her own control was felt to be the most appropriate study design.

Today we are going to continue this discussion, but also broaden it to include consideration of pacemaker and atrial defibrillator device interventions which may lend themselves to alternative clinical trial designs.

For AF ablation studies, the medical literature provides fairly well-characterized definitions of acute and

long-term success. However, for pacemaker and atrial defibrillator studies, success criteria have not been as well defined. During this panel meeting, we will ask you to discuss what might be considered clinically meaningful measures of device effectiveness for treating patients with AF.

Because pacemaker and atrial defibrillator AF therapies can programmed on versus off, investigations of these devices lend themselves to several potential study designs, some of which cannot be performed in AF ablation studies. During this panel meeting, you will be asked to discuss the advantages and disadvantages of several clinical trial designs for all three of these devices.

We can now proceed to the questions for the panel, and they're going to be read one by one as the panel discusses each one.

Thank you.

CHAIRPERSON CURTIS: I think what we can do is use the questions as a framework for the discussion for the rest of the afternoon, and we're basically going to split this up into two sections, one on pacemakers and implantable atrial defibrillators, and then we'll discuss separately the catheter ablation issues. So if we could go ahead and put up the first question? Discuss study design options below first for pacemakers and then for implantable atrial

defibrillators. We have the randomized controlled study, single-arm crossover study, and the single-arm prospective baseline period.

Anybody want to make any comments?

DR. DOMANSKI: Yes, I guess the first--it seems easier in a sense to think about what endpoints one wants to study first, but we've talked about it a little bit. I would express some enthusiasm in a setting like this for a randomized controlled study of the subject. I think part of the problem with anything that occurs over time is that there really are changes in the patients as time goes by, and I'm worried about for that, a little bit for that reason about using them as their own control.

So I would express some enthusiasm for being rigorous, and I think rigor demands a randomized controlled trial.

CHAIRPERSON CURTIS: Okay.

DR. SIMMONS: I don't know, I think just intuitively I like the crossover study better. You know, these patients, like you said, are changing. I mean, we haven't even addressed issues like drug therapy, how you're going to control for drug therapy, are you going to allow them to have differences in their clinidine levels and their amiodarone levels, and are you going to add drugs and take away drugs and treat their ischemia. So these patients are

going to be changing, but it does give you the opportunity in a single group to test in that particular individual is the therapy working or not.

So, I mean, if you had a treatment group that was randomized to no therapy, those patients may get treated differently, and so your randomized control group may not really be a control group to the group that you're actually studying.

DR. DOMANSKI: But usually--but what a trial--you know, there are certain things a trial can test and other things that it can't. It's very difficult to say we're going to test a therapy. What one does is test a strategy that involves a therapy. The distinction that I'm making is this: What one would do if one were saying--by the way, these are very difficult trials to do. Again, we've looked at this business of innovative therapies in a-fib, and it's a non-trivial question.

But, you know, what one would do is in an arm of a randomized trial devoted to maintaining sinus rhythm, what one would usually do is say that we are going to try for optimal standard therapy and then ask whether, in addition, the addition of an innovative therapy such as an implantable defibrillator impacts the endpoint. So that's how you usually do it.

The trouble with the crossover, again, is that

over time these patients change in ways that are difficult to fully define, but clearly they do in terms of their susceptibility to the a-fib, and the crossover suffers from not being able to resolve that.

DR. SIMMONS: Let's just suppose for a moment that the pacing therapy actually works, and so that group of patients might end up being on less medications, where if they'd been on more medication it might actually even work better. Or let's say that there's only a marginal difference and that you didn't institute a drug therapy because you weren't going to get a substantial clinical benefit, whereas in the control group, you know, you're going to be going all out, increasing drug therapies, doing everything you can, whereas with this one group if you cross over at least you've got the same physician taking care of the same patient, trying to treat--

DR. DOMANSKI: Well, again, I think what one has to do in any trial is test a strategy that can include or not include an innovative therapy. Kent?

DR. BAILEY: Yes, it seems to me that maybe we're talking about two different things here. Are we trying to show that the device does something, the procedure does something, i.e., maybe you can show that it reduces the amount of atrial fibrillation. And if that's the purpose, sure, random--crossover and you can see if there's more

atrial fibrillation in one period than another. But if you're trying to show a clinical benefit to the concept of reducing the amount of atrial fibrillation, then I think Mike is right; you want to try it on one group and not on another.

DR. HARTZ: I don't think you can do this except in a crossover fashion. I think every attempt should be made not to change any therapy during the two different on and off strategies. No attempt should be made--I mean, the patient should be studied in identical conditions in the on and off strategy, and probably several times, maybe a week on, week off, week on, week off. And only after accumulation of the data, whatever endpoints we decide on during that period of time, should then attempts be made to change medical therapy, because we don't know what we're studying yet. We've decided that those ten-minute periods don't mean anything. Maybe in doing a crossover maybe we will find that they are meaningful if the patient finds that they're having far fewer. But if one is in the off strategy trying to--the on strategy immediately trying to decrease drugs, we're not going to learn anything. That's my way to look at it. I don't think the randomized controlled study would show anything in this--

CHAIRPERSON CURTIS: Well, perhaps we need to have something of a discussion about the endpoints in order to

really intelligently say what kind of trial design you'd use. So let's talk about that a little bit. We started before. And the second question, would you put that up, Mitch?

Discuss whether reduction in occurrence of symptomatic, or symptomatic and asymptomatic episodes would be considered clinically relevant in demonstrating effectiveness of AF pacing therapies.

One of the articles in the packet that we got, the article by Page and Pritchett and coworkers, mentioned that there was a 12:1 ratio of asymptomatic to symptomatic sustained atrial fibrillation episodes. And so the total amount of atrial fibrillation burden is actually much more heavily weighted toward asymptomatic than symptomatic episodes.

So I think that really becomes a big issue, and I think we need to revisit what we started talking about before about what's a clinically relevant endpoint, because, I mean, the number of 25 to 35 percent reduction is kind of--that's very much in line what we look for with other kinds of therapies, you know, thrombolytic therapy, I mean, you'd like to see--or the number of MIs, that sort of thing. The 25 to 35 percent reductions in death and MI and revascularization need, that sort of thing, are very obvious clinical benefits to a patient. The question is whether a

25 to 35 percent reduction in number of episodes of atrial fibrillation really means something to a patient.

And, yes, I mean, we know that atrial fibrillation is bad, it's better off not to have it. But if you're talking about, say, a 30 percent reduction where 12 episodes are asymptomatic already, I don't know whether or not--you know, how much the patients are going to feel much different, and I don't think anybody here says we're going to be able to tell the difference in issues about anticoagulation, stroke risk, and all that sort of thing.

So what kind of endpoint do we really need? Number of episodes of a-fib, a-fib burden is measurable, and maybe the first thing we should talk about here is whether or not only symptomatic episodes should matter or whether the asymptomatics, too.

DR. BAILEY: What about the size of the atrium as an endpoint?

CHAIRPERSON CURTIS: Size of the atrium?

DR. HARTZ: Smoke in the atrium?

DR. BRINKER: Let's get back to this thing. I think that it would be nice and be quantifiable to do asymptomatic and symptomatic episodes. And, by the way, the 25 to 35 percent, whenever you see something like this, you have to be very suspicious that these numbers are taken solely from pilot experiences, and that's what you can

expect, and so that's the level that is going to be put in to be tested. So it's sort of a slam-dunk. And I'm not sure that that's the way we should use a clinical trial to reaffirm necessarily what's found in pilot studies. We want to see if it's clinically relevant.

And I would just say b, with the addition of some other kind of patient status. Mike, you know, brought up the specter again of the quality-of-life issue, and in some way, somehow getting grips on this may be helpful in this regard. I think if patients actually felt better--which may be independent of the number of short symptomatic episodes they have of atrial fib, or asymptomatic episodes but maybe interrelated, they felt better and you got a quantifiable reduction, that would make me more happy about the type of therapy. Certainly if there were objective signs of benefit such as if you were doing a controlled study and the group with this form of therapy had less growth in atria size than the group with just medical therapy, that would be very interesting. But I would be more than happy to recommend approval of a device that at a minimum made the patient--allowed the patients to feel better and that was objectively proven.

DR. SIMMONS: I think some of the things that Mike pointed out already was the quality-of-life assessment, some form of an exercise test to look and see if maybe these

people can actually exercise more often, longer. How about hospital admissions, admissions for congestive heart failure? I'm not so sure thromboembolic events--I mean, obviously you said you weren't too excited about that, but it kind of appealed to me following numbers of thromboembolic events.

DR. DOMANSKI: No, I think, of course, one would follow thrombo events, et cetera. It's just that I think to power a trial so that you had a likelihood of seeing the difference would require an inordinate number of patients. Of course, you'd follow them, and if there were a difference, there's a difference. But I think you shouldn't try to power a trial to do it.

CHAIRPERSON CURTIS: Go ahead.

DR. VETROVEC: One comment that really has only been touched on, and it comes back to the quality of life, and I would also favor B, because one of the goals of therapy, of medical therapy, is to stop these events. And one of the ways patients might feel better is in being able to reduce their medical burden, their medical treatment. And that might even be a potential part of the endpoint. Could they be on this therapy, this mechanical therapy, electrical therapy, and have their dosage reduced, removed, what have you. And many patients that--and I don't treat these patients all the time, but many of the patients I see

have a lot of side effects to the medication. So that might be a quality-of-life--a sort of indirect quality-of-life benefit that would really enhance the patient.

CHAIRPERSON CURTIS: The question is how do you handle that, though, because if you're changing drug therapy along the way--

DR. VETROVEC: Well, I think this is where the crossover trial would become very important to show that, I think, where the patient would be crossed over in their own treatment.

CHAIRPERSON CURTIS: And hopefully maintained on the same drugs, at least for that period of time.

DR. BRINKER: One of the realities is that this probably is only going to be effective in--the absolute amount of arrhythmia reductions is not going to be what we would like to see, 90 percent or 100 percent. It's going to be pretty much in the range that's been suggested, maybe a little bit more. So I don't know. If you can reduce it 50 percent on good medical therapy, it seems to me unlikely that one would want to give up some of that therapy, you know, and make up for some of that 50 percent reduction. I think it's going to be hard. If this were an alternative form of therapy, I think it would be better.

CHAIRPERSON CURTIS: One of the problems with the crossover design, though, goes back to what--there's the

term atrial fibrillation begets atrial fibrillation, and some people, you know, have also the concept that sinus rhythm may beget sinus rhythm, or at least that's what we'd like to think or hope. And so if you're going to have crossover designs, I mean, the longer somebody is in an effective therapy that reduces--that may reduce the likelihood that they will have any further episodes of atrial fibrillation, so by the time you switch them over to the other therapy, it may look good but it may be a false look like that. So that has to be considered in here.

All right. So there's some thought about--I think quantifying number of episodes is easy, it's doable, and certainly if you don't have any impact on the number of a-fib episodes, then there's no point here. I mean, you have to measure that. But it sounds like there's a consensus that that may not be enough to be meaningful to a patient. And I think quality of life is really an important issue that I would want to see measured.

I don't know if, you know, exercising a patient--atrial fibrillation being such an intermittent problem, I think what the patients are more concerned about are issues like palpitations or being, you know, able to stop what they're doing, those sorts of quality-of-life issues. If they come in and they're in sinus rhythm, they may do pretty well in a treadmill, but that doesn't really impact on what

happens in between when they have their other episodes. I would think quality of life would be more the issue.

DR. CHANG: Is it going to be pacemaker versus medication or no medication? Are we testing the pacemaker against the best therapy available or no therapy at all? That will make an impact because somebody may take too much medication, they may not do well on the treadmill even though they're in sinus rhythm. If they have a pacemaker and they don't have to take any medicine, they can do better.

CHAIRPERSON CURTIS: I would imagine, you know, stable, best medical therapy before you start into the trial, and then hopefully keep that stable through the duration of the trial.

All right. Do any of these comments then here go back to the trial design in terms of randomized controlled versus crossover?

DR. BRINKER: Can I just--

CHAIRPERSON CURTIS: Go ahead.

DR. BRINKER: Just some sort of feasibility questions here. The methodology of monitoring AF burden would require that the control group have an implantable device to monitor, basically an implantable Holter, which this device would presumably supply, right? So that everybody in a randomized study, if that's going to be--

everybody in the study will have to have device either on or off to monitor duration--AF burden. I mean, because you have to monitor it 24 hours a day every day that the thing is in, at least the asymptomatic ones.

DR. DOMANSKI: But, of course, that's only one design. I mean, the business of looking at burden, that is, time in, is only one. I mean, people have used time to first recurrence probably more commonly than anything else. That has the drawback of so what if you recur for five minutes six months from now. You know, two people recurring for five minutes six months from now, one of them may go on and have many, many episodes, and the other one may go on for another year without having an episode. And, clearly, those are two different results so that people tend to look at the number of recurrences and so forth.

I'm not sure--I think perhaps one might not be wedded to one single way of quantifying the atrial fibrillation because I think there would be a lot to be sid for not implanting devices in everybody and being able to do a trial without that.

You know, time to chronic atrial fibrillation is another one which is a big one.

DR. BRINKER: Well, these people may not develop chronic atrial fibrillation.

DR. DOMANSKI: Yes, they may not. Well, then, you

know, then you wouldn't hit that endpoint, of course.

CHAIRPERSON CURTIS: Well, I think a crossover design where you go three months on, three months off type of thing and having patients switch back and forth avoids--to approach patients and say, you know, we'd like you to be in a clinical trial and there's a 50 percent chance we're just going to keep following you on the current medicines you're taking with nothing else, people don't tend to get real excited about that.

On the other hand, if you say, you know, we'll implant the device and there's a 50 percent chance we're never going to turn it on, that's not too attractive, either.

So if you can get to, you know, well, you'll have a period of time where it's on and a period of time where it's off and we're going to compare the two, that's more palatable to most patients, I would think.

DR. BRINKER: I think it would be. One point that I can't defend, however, is the remote potential that putting one or two leads in the atria may be in some way in some cases arrhythmogenic in itself. And so if you had every patient with the lead system in, you might be not getting a real comparison between people who are treated medically and people who are treated with the device. That's the part I can't defend. I don't think it's likely,

but I can't defend it.

DR. DOMANSKI: Unlike the angina group, though, I'm not sure that the patient acceptability would be so low. I mean, the place where we saw this kind of thing, that is, defibrillator versus medical therapy, is in a trial like Abbott, for instance, and in other trials that were similar.

Now, of course, it's a different arrhythmia and all that. It's life threatening. It's a little bit different. But there we found that there were a group of people who didn't want to come into the trial because they might not get the device. But there was also another group that didn't want to come in because they didn't want the device. And so I'm not sure exactly how that would pan out, as a matter of fact.

DR. HARTZ: I'm not sure any IRB I've ever sat on would approve this study, to put devices in patients with the full intention of never turning them on.

DR. DOMANSKI: I wasn't suggesting putting them in with the intention of never turning them on. I was suggesting that one might want to have a design where people are randomized to standard therapy plus the device or standard therapy without the device. No, I agree with you. I wouldn't--no, no, I agree with you. I think you're right.

DR. BAILEY: I think if you do the crossover, then you're saying you're accepting the quantity of atrial

fibrillation as a valid surrogate endpoint, and you're giving up on the question of whether that produces a clinically meaningful result, other than symptomatic relief. And that's fine. You know, symptomatic status or a number of--but the point you brought up about what if what you do in the first six months has a persistent effect, then how do you interpret the crossover results.

CHAIRPERSON CURTIS: I think one way you do it is by not having the period of treatment be too long, because the longer you go, the more remodeling you potentially have. And some of that data has come up with the atrial defibrillators, where it seems that, you know, there's some suggestion that the longer the device is in, the less often it needs to be used, to some extent. So, you know, possibly limiting treatment periods to three months would be better than having it be longer than that because there might be more of an ongoing treatment effect after you switched.

DR. DOMANSKI: You know, it's an interesting thing. We had some--there was some enthusiasm inside of NASPE for looking at a study in which one tried to decide whether atrial fibrillation recurred less frequently if one took new onset of atrial fibrillation and cardioverted them immediately in the face of a negative TEE or anticoagulated them and then waited some weeks, that is, there was a concern about even a few weeks making a difference in terms

of electrical remodeling, and that kind of concern, of course, bears on a crossover study. I'm not sure that we really fully understand the importance of remodeling over relatively short periods.

DR. BRINKER: If you do a randomized study in which half the people get the device but don't get it turned on for six months and then they'll get it turned on, so then you'll have your six months, and then you'll have the other half who had it on from the get-go.

DR. DOMANSKI: Yes, well, that actually--let me just think through this, because I may be wrong. But it seems to me that that produces an asymmetry because what happens then is the group that didn't get it turned on perhaps had some electrical remodeling, now it's turned on and that's very different than the group that got it turned on right at the beginning that didn't get any electrical remodeling. I mean, you're--

DR. BRINKER: What do you mean by--I mean--

DR. DOMANSKI: I may be wrong about that, but it seems to produce an asymmetry.

DR. BRINKER: Think about that and we'll get back to you.

DR. DOMANSKI: Yes, okay. Play with that one.

[Laughter.]

CHAIRPERSON CURTIS: Just one announcement. There

is a Honda Civic in the parking lot, two-door, red, CPN-906, your lights are on, if that relates to anybody in here.

DR. HARTZ: Just to go back, I don't think we can avoid the issue of anticoagulation with Coumadin, and the FDA presentation is exactly right on. The most serious concern is stroke. We're talking only 6 percent at 60, what, 30 percent at age 80 or something like that, patients with atrial fibrillation? So in some way, the dose of Coumadin or changing to another form of anticoagulation, antiplatelet drug perhaps, and perhaps a combination of other therapies which we may discuss later on when we get into linear lesions, because there are some surgical series now that are ablating both atrial appendages on every single operation they do in the octogenarian population. So perhaps it will come to be that we'll add atrial appendage ligation through fluoroscopic devices to these protocols in the future. I don't know. But I think a main endpoint has to be stroke instance and Coumadin dose, and especially if you can decrease Coumadin dose in these patients, that would be a very hard endpoint.

CHAIRPERSON CURTIS: Well, I couldn't--to me, you would design these trials so that patients would be on Coumadin and stay on it through the trial and make sure their INRs were in the right range.

DR. HARTZ: Exactly. The point was made, too,

that Coumadin--that these patients were all going to be Coumadinized, no matter what. But our goal would eventually be, hopefully, with these devices and other forms of intervention to decrease the Coumadin dose, to avoid Coumadin in some of our patients in the a-fib population. So I think we should look at it. It should be a hard endpoint.

CHAIRPERSON CURTIS: Microphone?

DR. BAILEY: But that's going to be dependent on the practice, and if it's just based on what's happening in terms of atrial fibrillation, it's just a circular thing. So I don't see how that's an objective--

CHAIRPERSON CURTIS: I don't think it's an objective of this trial, but, you know, you can certainly count it. But whether you could decrease or get rid of Coumadin later on is a different issue.

DR. BAILEY: But what in a patient would you use to decide to stop having them on Coumadin?

CHAIRPERSON CURTIS: Yes, right now it would be a bleeding episode. But aside from that, I mean, that's something to, I think, be thought of later on.

The next question on the study endpoints I think we've touched on briefly. I want to see if there's anything else we want to cover. It's how should burden be defined. Is it time spent in AF, AT or both? Days in which a patient

has at least one episode or something else?

We've talked about number of episodes and decreasing that. Is there any better way to look at it, total number of minutes in atrial fibrillation? Time to first episode is something that's used commonly.

DR. BAILEY: I think it should be a combination of a duration and frequency.

DR. BRINKER: Well, what kind of information do we get from the device? Will it time the duration, the actual duration? And if it breaks for two beats and then goes back in, will it be able to differentiate that?

DR. GOLD: Typically, obviously, there are multiple different devices out there, but normally devices will mode switch after X number of beats, will then catalogue on a histogram the duration of that mode switch episode, and then it takes several beats to come out of that mode switch episode. So depending on how they program the durations going in and out, one or two beats of sinus rhythm will often not be detected by the device as a termination of an event.

DR. BRINKER: So duration's probably a safer endpoint than number of episodes if you want to really be precise about it.

DR. GOLD: Right. They can be very subtle going in out of the mode-switching type of transitions.

CHAIRPERSON CURTIS: Any other comments?

DR. CHANG: Just a technical question. How much memory storage does a pacemaker have? That will translate to how often you're supposed to interrogate that pacemaker. I know some of the older models, they have a limitation on the beams that will store the frequency and duration of the atrial fibrillation.

DR. GOLD: I'm told by my experts it's about 120K RAM that are in most of the modern pacemakers. They can store a lot of information right now.

CHAIRPERSON CURTIS: Okay. The next question relates to implantable atrial defibrillators. Is atrial shock therapy effectiveness best measured by the ability to terminate the episodes, or what other endpoints do you think might be appropriate? I think termination of an episode is the appropriate thing to look at. And if that weren't true, then what else would you substitute for it?

DR. DOMANSKI: Yes, I actually agree with that. There are a number of reasons why one might choose to terminate an episode. So a question you could ask is, given that I want to terminate it, how good is this device at doing it? And it would be reasonable to market a device, it seems to me, for that purpose.

DR. BRINKER: Well, you know, one--this is a trick question because, obviously, you want the device to

terminate the arrhythmia. But there is the actual termination of an atrial fibrillation episode, and then there is effective termination of an episode. So if you had a device, for instance, that would terminate atrial fib and then a minute later you'd go into atrial fib and then it would terminate it again, and then a minute later you'd go back and it would terminate it again, eventually it will either stop because of the algorithm that governs its stopping or the battery will wear out and become ineffective.

So there is one thing--the strategy of the atrial defibrillation is an issue other than its success at terminating atrial fibrillation. So I think somewhere in the back of the mind and in the evaluation process, one should evaluate the strategy of an implantable atrial defibrillator in patients with atrial fibrillation in addition to the effectiveness in which it will terminate a specific atrial fibrillation episode.

CHAIRPERSON CURTIS: I think if you had repeated episodes and the patient got shocked multiple times, quality of life probably wouldn't be too good. So we might--

DR. BRINKER: But a questionnaire is always perfect.

CHAIRPERSON CURTIS: Yes.

DR. DOMANSKI: It also depends on what you market

the device for, I mean, how you label it, I suppose.

MR. DILLARD: Jim Dillard. Could I ask for a clarification? You just made the point that it's the strategy of atrial fibrillation and then the effectiveness. Is there some additional guidance you could give us on the difference between the two of those and how would we make that differentiation?

DR. BRINKER: Well, yes, I mean, there's a--you've made this for hundreds of years. As long as the FDA has been in business, we've been told about there's a difference between--what was it?--a clinical utility and effect. So that if I put a stent in a patient in the coronary artery, I know that that stent will open up the artery. But you made us prove clinical utility. So just carry that parable with you.

[Laughter.]

DR. BRINKER: In other words, I know that an atrial defibrillator will defibrillate a fibrillating atrium. That's great. Now, is that--the clinical utility of that strategy is another issue, and there are a lot of little innuendoes to what will make this a clinically useful thing other than its ability to terminate an index rhythm and somehow this has to be thought out at probably more depth than, you know, this panel meeting would allow. But I think it's something to put in the back of your mind.

MR. DILLARD: Jim Dillard. Not to be belligerent here and press the issue, could you give me some bullet points that might be of consideration when we're talking about those things to look at? I mean, while not getting into depth, but some things that we might want to look into in terms of what that effectiveness/clinical utility might be?

DR. BRINKER: Well, I would guess one thing might be the need--either the need for--if you have a control group of some sort, whether patients who get defibrillated actually have less visits to the hospital for a definitive transthoracic defibrillation or a special programmed higher-energy defibrillation, whether the device turns out to--whether the strategy involves recurrent episodes of atrial fibrillation so that many patients are subject to a number of shocks externally--internally before they may go to the hospital or before they get some resolution, and whether the device actually will definitively terminate a--not just one episode but use a broader definition of an episode of atrial fibrillation that might be for a 24-hour period or something like that.

And I'm not an AF expert, but I would want to know that the strategy is clinically utilitarian.

DR. CHANG: I think the atrial defibrillator is designed to terminate atrial fibrillation episodes. I think

the endpoint should be judged the termination of AF and the absence of a recurrence after a reasonable time--no, not five seconds, maybe a minute or half a minute, just like a ventricular defibrillator is used to shock patient out of a VF and the patient goes into VF and that is not the inefficacy of the device.

I don't know what the time interval is, you know, the atrial fibrillation recurs after one second and certainly it's not inefficacy, and if it's five seconds, I don't know. Thirty seconds--

DR. HARTZ: You need the characteristics of the shock, too, because obviously the eventual goal would be to improve the electrode so that the patient would have less of a sense of pain. So joules, duration, whatever. I don't know how you measure all that stuff, but it's important.

DR. CHANG: I think all those people who consented to have an atrial defibrillator put in must be highly motivated.

DR. HARTZ: Yes.

DR. VETROVEC: Somehow I think somewhere in here, in the quality of life--and I've said this before, but I won't get off of it, I guess. But there's got to be some comparison to medical management in the sense of if you can reduce medical management, the patients may feel better. And I think that gets back at what you keep saying, Is the

patient better? And the patient may be no better in terms of the numbers they measure, but if they have to take less drugs and have the same clinical efficacy and feel better, then they're going to be better. And somehow that has to be built in there.

DR. DOMANSKI: Well, that's, of course, the--I'm not actually--I sound today like I'm a big enthusiast about quality of life. Actually, I prefer harder endpoints. But where they're absent, the measures of quality of life, in fact, integrate just the sort of things you're talking about.

DR. SIMMONS: The other thing, when you're mentioning about clinical utility, something that Anne mentioned earlier, you know, as far as remodeling of the atrium, certainly secondary endpoints that could be measured are the amount of AF burden, the number of shocks over time; the percentage of time the patient actually spends in a-fib may actually get less as the defibrillators--and that may prove or disprove any type of clinical utility, too.

DR. BRINKER: Yes, I think all those pieces of evidence are important. But I would want them in addition to evidence that it just converts the arrhythmia, which was the issue on the line. I don't think that in and of itself would be adequate for this form of therapy.

DR. BAILEY: Actually, if the shocks were painful,

it could train the patient to change their lifestyle so that they can avoid atrial fibrillation over time.

DR. BRINKER: Well, they should have had that training when they come into the hospital to get transthoracic shocks. And if they haven't learned by now, I'm not sure that an internal device will help.

DR. DOMANSKI: The record will have to show that generally lifestyle changes by the patients don't help.

CHAIRPERSON CURTIS: Let's go on to number 5. Discuss whether your expectation for a clinically relevant percent reduction in AF episodes would be altered by the risk/benefit profile for pacing therapy. So I suppose this gets at if there was some increased risk by implanting the device itself or some safety issue there.

In terms of the atrial pacer, you may be talking about an additional lead or a different location of a lead, and I have a hard time thinking that that's going to make a whole lot of difference to a patient. An atrial defibrillator, you've got different kind of lead configurations there.

DR. CHANG: Would that be a coronary sinus catheter or lead?

CHAIRPERSON CURTIS: Could be.

DR. CHANG: And the removal of it would be very difficult.

CHAIRPERSON CURTIS: It's already--some of those issues have come up with other kinds of pacing therapies, and every now and then, yes, it's going to have to come out. But so far I don't think that's really--I wouldn't expect that to wind up being a big issue. I have a hard time thinking of what could happen safety-wise that would change our discussion about efficacy endpoints.

DR. BRINKER: I mean, the ratio is what is important. There will always be some price to pay in terms of patient morbidity and rare mortality for a patient receiving an implantable device such as this. And the question is: Is the benefit that is gained from that form of therapy worth that small price to pay? And I guess it--for instance, is a reduction in the number of AF episodes by 25 percent and no other clinical correlate worth having a device that may become infected or requires a surgery or a lead explant? For the atrial defibrillator, it would be a reduction in AF episodes, but it may be a reduction in duration of fixed atrial fibrillation. And is that worth the morbidity of the implant and in this case the pain of the defibrillation?

And so I think those are issues that we have to help the sponsor have a protocol that would demonstrate to you that there is a--in the risk/benefit ratio, even a small risk becomes unacceptable if there's no clinical benefit.

MR. DILLARD: Can I maybe--Jim Dillard. There was kind of a more expanded question to this that may help clarify exactly what we want, and I just thought I might read it. During the July 1998 Circulatory System Devices Panel discussion of AF ablation clinical trial design, the panel recommended that sponsors demonstrate device effectiveness by showing a clinically significant reduction in frequency of symptomatic AF episodes. The panel suggested at that time that 50 to 75 percent reduction per patient would be clinically relevant for AF ablation; however, the risk/benefit profile--and I think this gets really to the subpart of this question--may be significantly different for pacing therapy as compared to ablation therapy. And in the medical literature, one of the risks is that major complications occur must less frequently during pacemaker implantation and follow-up as compared to AF ablation procedures, and the benefit--at this time there is very little conclusive data comparing the benefits of pacing to the AF ablation kind of therapy.

And so I think this is really where we get to kind of the summation question, which is, Please discuss whether your expectations for a clinically relevant percent reduction in AF episodes would be altered by this difference in risk/benefit profile, and it certainly goes to the difference, again, in risk level potentially when we're

talking about ablation types of procedures. And then is there a way to look at these differently based on that risk? And is there some guidance you can give us, I think, in the pacing area that might be similar to the type of guidance you've given us in the ablation area.

DR. BRINKER: I think you're right. You know, as the ante is raised by the intervention that you perform, you would like a better pot basically to take in in that game. So I think it's likely that if ablation is not made very safe and easy--and it's going that way, actually--then one would envision some sort of staged approach to the patient with problematic atrial fibrillation, in which each of these may have a role.

On the other hand, if ablation was very safe and very effective, it would be--it would raise what you would want to see from an alternative form of therapy on the clinical point of view, but for the regulatory point of view--I mean, my feeling is if there is an acceptable--based on what we know now--risk/benefit ratio, clinical benefit, then it should be approved. And, in general, the risk for the involved atrial ablation kinds of therapies, time duration and the relative success rate is not so overwhelming that this is--that atrial--that pacing modalities and defibrillation still don't have a significant role. And I would accept a lesser degree of success rate in